What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? A systematic review and economic evaluation

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Scientific summary

Cytisine and varenicline for smoking cessation

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Background

Tobacco smoking is one of the leading causes of preventable deaths worldwide. Nearly one-fifth of adults in the UK regularly smoke cigarettes. The ill-health associated with smoking costs the NHS over £3B every year. Stopping smoking is difficult; however, it can significantly reduce the risk of smoking-related illnesses such as heart disease and cancer. A number of interventions are available that can help people to quit smoking. These include nicotinic receptor partial agonists such as varenicline or cytisine. Varenicline is a synthetic product licensed for use in the UK as an aid to smoking cessation. Cytisine is a naturally occurring product, derived from the seeds of the plant *Cytisus laborinum* L. (golden rain acacia), which is not currently licensed for use in the UK, although it has been available as an aid to smoking cessation in a number of Eastern European countries for over 40 years. Reviews of these interventions have shown them to be more effective in helping people to quit smoking than placebo. Concerns over the safety of varenicline have been raised; however, reviews have produced inconsistent findings. To date there have been no head-to-head trials comparing the clinical effectiveness of varenicline and cytisine. Consequently, there remain outstanding questions regarding which of the two drugs shows greater clinical efficacy. In addition, although cytisine is reported to be cheaper than varenicline, it is unclear which of the two drugs is the most cost-effective.

Objectives

The main research question addressed by this assessment is 'What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation?' The specific objectives of the assessment are:

- to review the evidence on the clinical effectiveness and safety of cytisine for smoking cessation compared with varenicline
- to develop an economic model to estimate the cost-effectiveness of cytisine and varenicline within the context of NHS smoking cessation services
- to provide recommendations based on value of information analyses whether or not a head-to-head trial of cytisine and varenicline would represent effective use of resources and, if so, the recommended number of smokers in each arm.

Methods

Clinical effectiveness methods

The inclusion criteria for the review were as follows:

- Population: adult smokers.
- Interventions and comparators: cytisine, in any formulation, or varenicline, in any formulation. In the anticipated absence of data from head-to-head studies of cytisine and varenicline, any other comparators [e.g. placebo, nicotine replacement therapy (NRT), bupropion] were considered that would allow an indirect comparison to be made.
- Outcomes: the primary outcome was abstinence at a minimum follow-up of 6 months. Secondary outcomes were common adverse events, namely abnormal dreams, headache, and nausea and insomnia.
- Study design: randomised controlled trials (RCTs).

A recent good-quality Cochrane review of nicotinic receptor partial agonists was identified. Data for efficacy and adverse events from this review were used to evaluate the clinical effectiveness and cost-effectiveness of cytisine and varenicline. In addition, a comprehensive search was undertaken in order to update the data in this review and use both sets of data to inform, where appropriate, indirect comparisons between the two interventions. The updated search was conducted across 12 electronic databases, including MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature and The Cochrane Library, for the period from December 2011 to January 2013. Bibliographies of any newly identified trials were hand searched to identify any further trials. Two reviewers sifted potentially relevant studies independently and inclusion decisions were agreed among the broader research team with reference to the project's clinical experts. The methodological quality of the newly included studies was assessed using the Cochrane risk of bias tool. The results of included studies were synthesised using both narrative and statistical methods.

Methods of data synthesis

Abstinence data and adverse events data were synthesised using a network meta-analysis. The analysis combined evidence across studies in which there was at least one treatment in a study that was common to at least one other study. A random (treatment)-effects model was used to allow for heterogeneity in treatment effects between studies.

Cost-effectiveness methods

As detailed in the protocol, the model structure was based on the Benefits of Smoking Cessation on Outcomes model. The economic analysis was focused on a population of smokers in England and Wales aged 18 years or older who are motivated to quit smoking. It evaluated the cost of the standard doses of both cytisine and varenicline, and was modelled on a hypothetical cohort of 10,000 smokers, with each smoker assumed to make a single quit attempt, assisted by either varenicline or cytisine.

Results

Results of clinical effectiveness review

Twenty studies from the existing Cochrane review were included in the review and a further three studies were identified by the updated search. The studies comprised 10,610 participants. Twenty-one of the studies evaluated varenicline, with the remaining two studies evaluating cytisine. Comparators included placebo, NRT and bupropion. Overall, the quality of the studies was good, with no studies judged to be at high risk of bias.

As no head-to-head trials comparing cytisine with varenicline were identified, indirect comparisons were made using network meta-analyses. These showed that cytisine produced the greatest effect on abstinence than placebo and had the highest probability of being the most effective intervention.

Standard-dose varenicline treatment was associated with significantly higher rates of headache, insomnia and nausea than placebo; there was no significant difference in the rates of abnormal dreams. There were no significant differences in rates of headache or nausea between cytisine and placebo; data were not identified for abnormal dreams or insomnia.

Results of cost-effectiveness analyses

Outputs from the economic model estimated that cytisine treatment would produce more mean life-years and quality of life-adjusted years, and lower mean lifetime costs, than varenicline treatment and is, therefore, expected to dominate over varenicline. The economic analysis is driven by the relative effectiveness of cytisine and varenicline. The treatment that generates the greatest number of quitters will have the best long-term health outcomes, as smoking cessation produces reduced costs associated with longer-term conditions associated with smoking. Based on the current available data, if treatment costs were equal for cytisine and varenicline, there is a greater probability that cytisine will be the optimal choice. However, there is uncertainty in this decision and, owing to the very large numbers of smokers receiving NHS treatment for smoking cessation each year (around 800,000 individuals), the value of further information on the relative effectiveness of both treatments is high.

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Expected value of sample information analyses indicated that a RCT with 1000 smokers per arm comparing cytisine with varenicline would represent efficient use of scarce resources and would allow more robust conclusions to be made regarding the relative efficacies of the two treatments.

Discussion

Previous systematic reviews of varenicline and cytisine have produced findings consistent with this review. Varenicline has been shown to increase smoking cessation by around twofold, and reviews of cytisine show modest efficacy rates compared with placebo, although it is acknowledged that only two high-quality trials of cytisine with a minimum of 6 months of follow-up have been conducted to date, and that absolute quit rates are low. Trials in real-world settings such as pre-operative surgeries or using participants with underlying medical conditions have shown the efficacy of varenicline to be stable. No such trials of cytisine that study subpopulations have been conducted to date.

The results of the network meta-analysis showed varenicline to be associated with greater risk of some common adverse events than cytisine, although there was no difference in the risk of serious adverse events and data were not available for cytisine for all adverse events. Overall, the safety evidence in the current review was weak and a full safety review was not undertaken. Previous reviews of varenicline for smoking cessation have highlighted potentially serious adverse effects, although the results of these reviews are not consistent. Conflicting findings for cardiovascular events have been reported and reviews of trial data have shown no increased risk of serious adverse neuropsychiatric events. These recent systematic reviews use only trial data, and these may not capture all adverse events owing to strict exclusion criteria. Practitioners should be aware when making treatment decisions for individual smokers that adverse events may be more likely in those with underlying medical conditions. A full safety review of cohort studies for both varenicline and cytisine is recommended.

We believe that this research is the first to explicitly evaluate the benefits associated with undertaking a RCT of cytisine compared with varenicline. Cytisine is currently unlicensed for use in the UK and, therefore, the cost may increase if the manufacturer were to incur costs associated with fulfilling licensing requirements. However, the fundamental conclusion that a head-to-head trial of cytisine compared with varenicline is needed remains unchanged.

Conclusions

On the basis of the evidence included in this review, varenicline and cytisine are both effective interventions to aid smoking cessation when compared with placebo. Cytisine showed the greater expected efficacy and was estimated to be the more cost-effective intervention. However, uncertainty still remains and a head-to-head RCT of 1000 smokers is recommended and estimated to be an efficient use of resources.

Study registration

The study was registered as PROSPERO CRD42012003455.

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